

Autosomal dominant retinitis pigmentosa mapping to chromosome 7p exhibits variable expression

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Abstract

The genetic locus causing autosomal dominant retinitis pigmentosa (adRP) has recently been mapped in a large English family to chromosome 7p. Eight affected members of this family were studied electrophysiologically and psychophysically with dark adapted static threshold perimetry and dark adaptometry. The phenotypes observed fell into three categories: minimally affected with no symptoms, and normal (or near normal) electrophysiology and psychophysics; moderately affected with mild symptoms, abnormal electroretinograms, and equal loss of rod and cone function in affected areas of the retina; and severely affected with extinguished electroretinograms and barely detectable dark adapted static threshold sensitivities. The mutation in the gene on 7p causing adRP in this family causes regional retinal dysfunction with greatly variable expressivity ranging from normal to profoundly abnormal in a manner not explained by age.

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Inherited disorders causing photoreceptor degeneration with nightblindness, reduced peripheral vision, and preservation of central vision until late are known collectively as retinitis pigmentosa (RP).¹ RP may be inherited in an autosomal dominant (adRP), autosomal recessive, or X linked manner. The incidence of RP in the United Kingdom is approximately 1 in 5000, with adRP accounting for 24% of families and 38% of cases.²

In adRP both allelic and non-allelic genetic

heterogeneity exist.³⁻¹¹ Mutations in the rhodopsin gene (RHO) on chromosome 3 account for approximately 30% of adRP,¹² with over 50 mutations having been reported.¹³ Mutations in the gene encoding RDS-peripherin on chromosome 6 have also been implicated in adRP.^{9,14-18} A third locus has been provisionally mapped to chromosome 8⁸ and a fourth to chromosome 7q.¹⁰ Recently, our group has mapped a fifth adRP genetic locus to chromosome 7p.¹¹

In this report, we describe the electrophysiological and psychophysical features of retinal dysfunction in chromosome 7p-adRP¹¹ in affected family members different from those described in a previous study which used older generation instrumentation.¹⁹ We expand the known range of phenotype expression observed in chromosome 7p-adRP.

Methods

Some details of this large, nine generation English family have been described previously.^{11,19,20} The severity of disease varied widely between affected members. We studied eight patients (Fig 1) with the haplotype on chromosome 7p linked with adRP¹¹ who were not studied previously.¹⁹ They were selected on the basis of having sufficient visual function to warrant documentation using electrophysiological and psychophysical techniques. The right eye of each patient was studied. Patient details are summarised in Table 1. Patients VIII-22, VIII-23, and VIII-24 are siblings. Patient VII-45 is the mother of VIII-52.

Subjects underwent dark adapted electroretinographic testing (ERG) using a standard protocol.²¹ Blue flashes were used for eliciting rod dominant responses, red flashes for resolving cone responses from rod responses, and white for mixed cone and rod responses as well as cone flicker responses. In contrast with our previous study in which dark adapted static threshold testing was performed at only 22 points without dark adaptometry,¹⁹ in this study both dark adapted static threshold perimetry and dark adaptometry were performed using a newer

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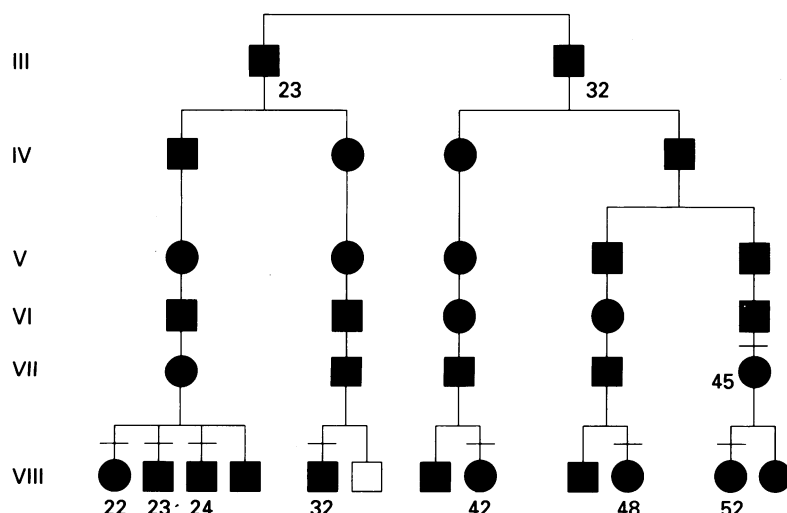


Figure 1 Abbreviated family pedigree (see Inglehearn et al.,¹¹ Moore et al.,¹⁹ and Jay et al.,²⁰ for more details of this nine-generation family). Solid boxes or circles indicate affected males and females, respectively. Horizontal notches indicate individuals studied in this report. Roman and arabic numerals indicated respectively, generation and position numbers in refs 19 and 20.

Table 1 Patient characteristics

Patient	Sex	Age	VA	Subjective symptoms	
				Night blind	Field constriction
VIII-23	M	43	6/6	No	No
VIII-24	M	45	6/6	No	No
VIII-48	F	25	6/6	No	No
VIII-22	F	46	6/6	Yes	No
VII-45	F	51	6/6	Yes	No
VIII-52	F	26	6/6	Yes	No
VIII-42	F	38	6/12	Yes	Yes
VII-32	M	49	6/6	Yes	Yes

Table 2 Flash electroretinographic results

Subject	Blue run 12*		Red run 18*		White run 20*				30 Hz flicker*	
	b Wave		b Wave		a Wave		b Wave		b Wave	
	Amp	Imp	Amp	Imp	Amp	Imp	Amp	Imp	Amp	Imp
Normal mean	319	57	91	48	132	22	384	45	43	29
Normal limit	141	69	16	56	41	25	208	49	10	32
VIII-23	220	58	150	48	200	22	240	46	35	29
VIII-24	260	58	225	54	100	22	280	49	45	29
VIII-48	145	60	75	56	40	27	150	56	30	29
VIII-22	40	56	25	50	Flat		40	46	12	32
VII-45	Flat		Flat		Flat		Flat		Flat	
VIII-52	Flat		Flat		Flat		Flat		Flat	
VIII-42	Flat		Flat		Flat		Flat		Flat	
VIII-32	Flat		Flat		Flat		Flat		Flat	

*Refers to runs 12, 18, 20, and 30 (flicker) in Jay *et al*²⁰. In run 18, only the cone b wave was measured. Amp=amplitude in μ V; Imp=implicit time in ms. Normal limit=normal mean -2 SD for amplitude and normal mean $+2$ SD for implicit time.

generation, modified Humphrey automated perimeter.^{22,23} Under dark adapted conditions with dilated pupils, cone and rod sensitivities were determined in an unlit bowl with size 5 red and blue test stimuli, respectively, using a standard 30-2 program. Two points were then selected for dark adaptometry. Following exposure to bright white light sufficient to bleach 95% of rhodopsin, the recovery of sensitivity to size 5 blue test stimuli was followed over time.

Results

Patients VIII-23, VIII-24, and VIII-48 were all asymptomatic. In one (VIII-48), the only abnormality was a delayed and reduced ERG amplitude to bright white flashes (Table 2), her other ERG responses and sensitivities (Fig 2C and Fig 4A) being normal. In the other two, the results of all functional tests were within normal limits (Table 2, Fig 2A and 2B). These patients all had scattered intraretinal bone spicule pigmentation and the haplotype linked with chromosome 7p-adRP.

Patients VIII-22, VII-45, and VIII-52 were symptomatic with reduced ERG responses (Table 2). Dark adapted static threshold perimetry revealed peripheral depression in cone and rod mediated sensitivities which were affected in the same areas to a similar degree with preservation of sensitivities centrally (Fig 3). These individuals demonstrate regional²⁴ or class²⁵ functional loss. While the final thresholds for the cone and rod components of the dark adaptation curve were elevated, the rates of dark adaptation were normal (Fig 4B, C, and D).

Patients VIII-42 and VII-32 were severely affected with symptoms of early onset, extinguished ERG responses, and barely detectable dark adapted static perimetric sensitivities (Fig 5). These individuals were too severely affected to undergo dark adaptometry testing.

There is no recognisable pattern of severity of disease in the families. There is no correlation of the degree of functional loss between siblings or between children and their parents or the sex of the affected parent.

Discussion

By history alone, this family seems to exhibit incomplete penetrance, with RP appearing to 'skip' generations.²⁰ Assessment of penetrance, however, varies with the level of ascertainment and the sensitivity of testing systems in the detection of retinal functional losses. In our previous survey of different members of this family,¹⁹ we studied one asymptomatic obligate carrier (VII-41) who exhibited reduced amplitude electroretinographic responses and peripheral constriction on Goldmann perimetry. On this basis it was considered that there was variable expressivity rather than incomplete penetrance. Patients VIII-23, VIII-24, and VIII-48 had minimal fundus changes; two of the three lacked any delay in cone implicit times and none had elevated dark adapted static perimetric rod thresholds, both of which have reported as being sensitive indicators of mild retinal dysfunction.^{19,26,27} It is possible that these individuals

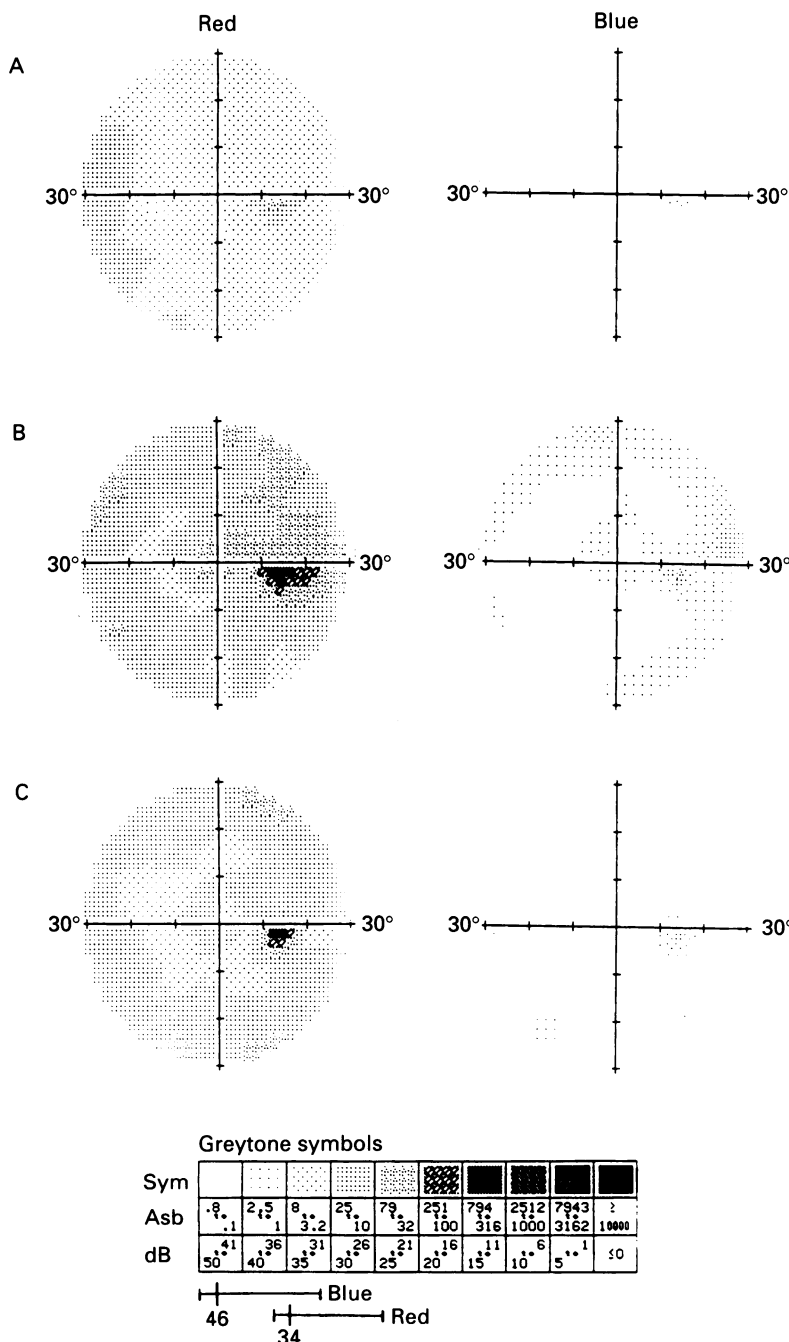


Figure 2 Dark adapted static threshold perimetry for patients VIII-23 (A), VIII-24 (B), and VIII-48 (C). Average sensitivities in decibels (dB) with bars indicating range for normal individuals are indicated on the greyscale at the bottom.

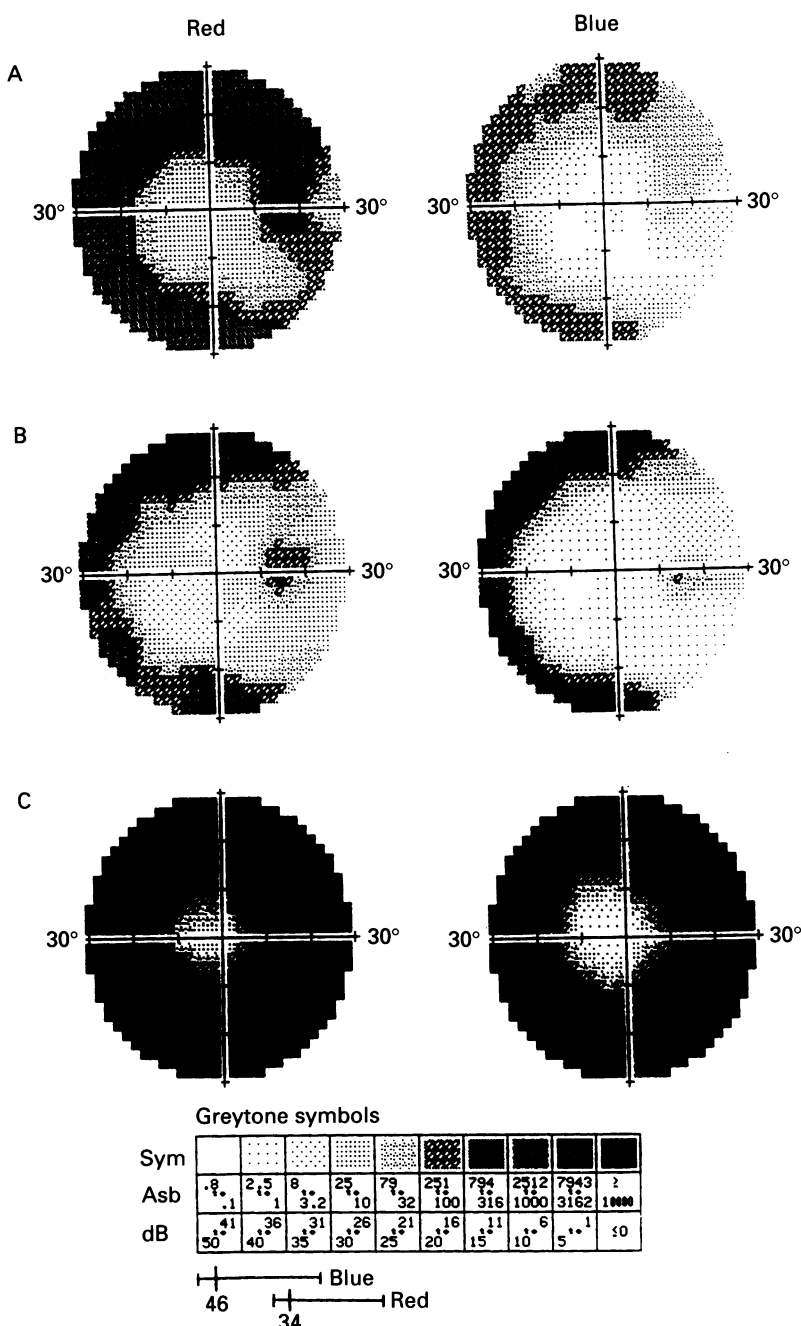


Figure 3 Dark adapted static threshold perimetry for patients VIII-22 (A), VII-45 (B), and VIII-52 (C). Average sensitivities in decibels (dB) with bars indicating range for normal individuals are indicated on the greyscale at the bottom.

would have been indistinguishable from normal using currently available examination techniques had they been seen in the second or third decade of life at a time when genetic counselling is most important. Thus, this family highlights the potential difficulty in distinguishing between incomplete penetrance (an all or none phenomenon) and variable expressivity (a graded phenomenon).

The degree of retinal degeneration was variable in a manner not explained by age. The eight patients studied varied from minimally affected and asymptomatic with only scattered intraretinal bone spicules but normal ERG responses and dark adapted psychophysics to severely affected with extinguished electroretinograms and barely detectable dark adapted static perimetric sensitivities. Between these two extremes were moderately affected members with recent

symptoms, reduced electroretinographic responses, and psychophysical evidence of regional²⁴ or class 2²⁵ retinal functional loss, as opposed to diffuse²⁴ or class 1²⁵ functional loss.

The pattern of concentric, regional retinal functional loss (Fig 3) differs from the regional patterns seen in adRP associated with mutations in the RHO gene.^{23, 28-37} In all but one patient with a rhodopsin mutation,²³ the inferior retina was preferentially compromised in an altitudinal distribution. The one exception was a RHO gene insertion causing retinal functional loss greater inferiorly but not in an altitudinal distribution.²³ In addition to regional²⁴ or class 2²⁵ retinal functional loss, allelic mutations in the RHO gene can cause diffuse²⁴ or class 1²⁵ functional loss.¹³ Since many of the functional attributes of rhodopsin are known,³⁸ it is possible to formulate hypotheses concerning the pathogenesis of disease. Although the genetic locus responsible for adRP in this family has been mapped to the short arm of chromosome 7,¹¹ the responsible gene has yet to be identified.

These families present a particular challenge in genetic counselling since at a time at which members are having children the phenotype may not be recognisable. For this reason, it is not possible to exclude the possibility of their having affected children or of excluding genetic risk in a member whose parents are apparently normal. This is all the more important since mild disease or a lack of disease in the parent does not preclude severe disease in the children. Knowledge of the locus of the causative gene allows accurate counselling if the family is informative for the available genetic markers. Once the mutation is determined the genetic status could be identified with certainty.

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Figure 4 Dark adaptometry. Large circles indicate patient responses; small circles for age-matched normals. Prebleach measurements were made before time 0. Two points were evaluated based upon the results of dark adapted static threshold perimetry (Figs 1–3). (A) Patient VIII-48 was studied at positions $+9^\circ, +9^\circ$ (solid circles) and $-9^\circ, -9^\circ$ (open circles); (B) patient VIII-22 was studied at positions $-9^\circ, +15^\circ$ (solid circles) and $+9^\circ, -15^\circ$ (open circles); (C) patient VII-45 was studied at positions $+15^\circ, -15^\circ$ (solid circles) and $-15^\circ, +15^\circ$ (open circles); (D) patient VIII-52 was studied at positions $-3^\circ, +9^\circ$ (solid circles) and $-9^\circ, 0^\circ$ (open circles).

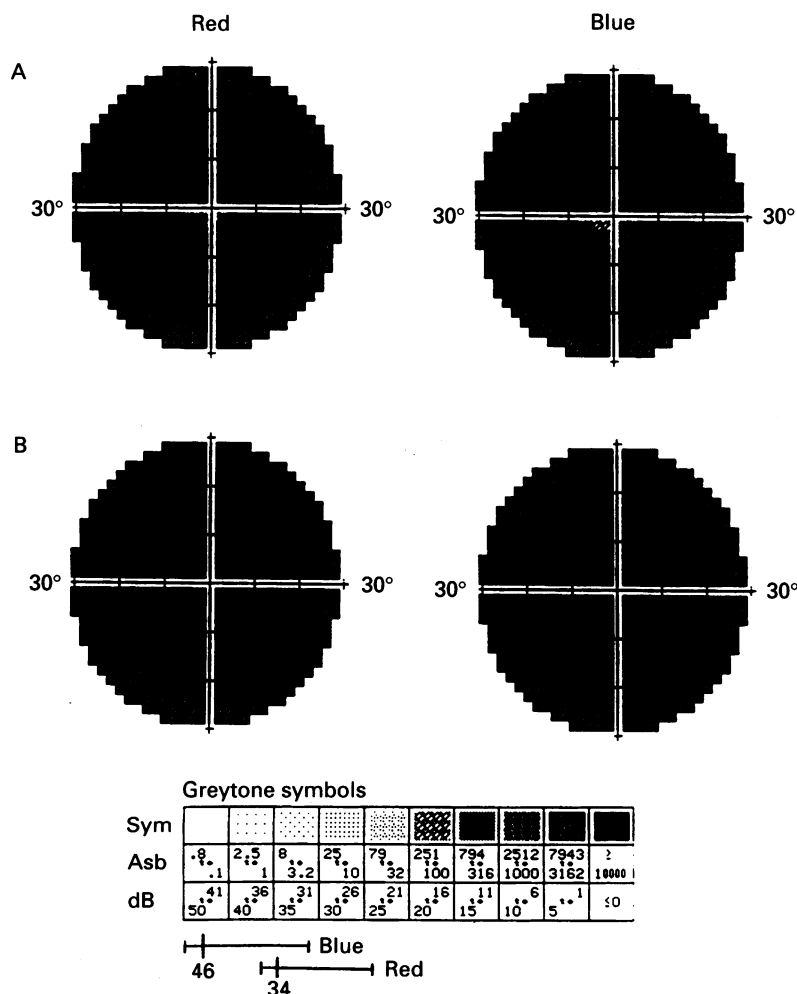
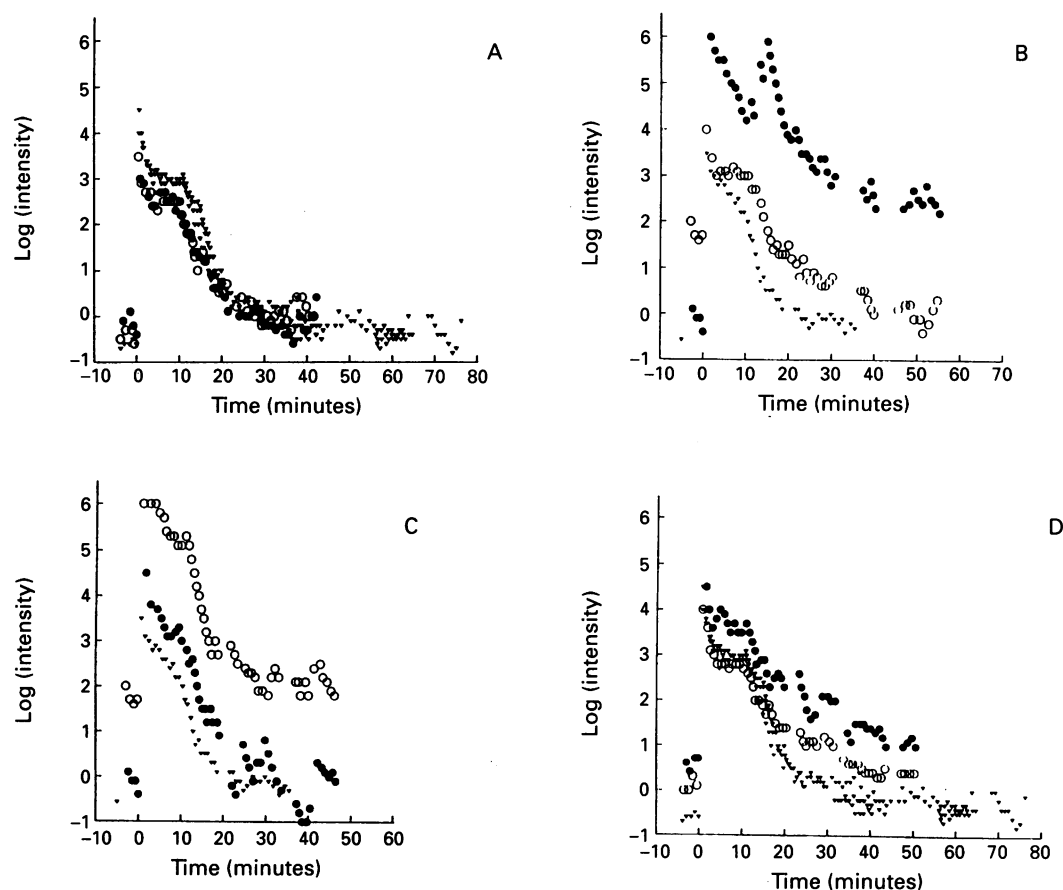


Figure 5 Dark adapted static threshold perimetry for patients VIII-42 (A) and VII-32 (B). Average sensitivities in decibels (dB) with bars indicating range for normal individuals are indicated on the greyscale at the bottom.

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